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Effects of Histamine on Coronary Hemodynamics in Humans: Role of H_1 and H_2 Receptors

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To evaluate whether histamine exerts a direct effect on coronary hemodynamics in humans, and to investigate the role played by H_1 and H_2 receptors in this response, intracoronary saline solution or histamine (4 μg) was administered in 10 patients with normal coronary arteries during diagnostic cardiac catheterization. Histamine injection was repeated after intravenous cimetidine (400 mg) and diphenhydramine (10 mg). The electrocardiogram, arterial pressure and thermodilution coronary blood flow were continuously monitored during and for 40 seconds after each injection.

Immediately after histamine injection there was a significant increase in coronary blood flow (65 ± 6%) and a decrease in coronary vascular resistance (−40 ± 3%) (both $p < 0.001$), with minor changes in the RR interval and the mean arterial pressure. H_2 receptor blockade with cimetidine did not affect these changes, while H_1 receptor blockade with diphenhydramine significantly reduced the histamine-induced increase in coronary blood flow and the decrease in coronary vascular resistance (26 ± 6%, $p < 0.005$ and −18 ± 5%, $p < 0.001$, respectively). Twenty to 30 seconds after histamine injection, a significant decrease in mean arterial pressure (−17 ± 2%, $p < 0.001$) and in the RR interval (−4 ± 1%, $p < 0.01$) was observed. These changes persisted after H_2 receptor blockade with cimetidine, but were completely abolished after H_1 receptor blockade with diphenhydramine. In each case coronary and systemic hemodynamics returned to normal within 40 seconds of the injection.

Therefore, in patients with normal coronary arteries, histamine induces a direct dilation of the small resistance coronary arteries, regardless of myocardial metabolic requirement, that is predominantly, but not completely, mediated by H_1 receptors.

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Exogenous (1,2) and endogenous (3) histamine produces significant cardiovascular effects in humans that are mediated by specific H_1 and H_2 cardiovascular receptors (4). Although histamine is known to induce coronary vasodilation or vasoconstriction in animals, depending on species, dose and study design (5–9), the direct effects exerted by histamine on the human coronary circulation are less understood. Histamine is contained in large amounts in the heart (10) and can be released by immunologic (3,11) and nonimmunologic stimuli (12,13). In humans, histamine is present in coronary artery walls, particularly in patients with coronary artery disease (14) and in those with variant angina (15). In vitro studies on human large coronary arteries have shown that histamine induces a coronary vasoconstrictor effect that is enhanced by the atherosclerotic process (14,16). This vasoconstriction is due to activation of H_1 receptors; H_2 receptors subserve vasodilation (17). However, these results can hardly be extrapolated to the in vivo coronary circulation and to subjects with normal coronary arteries. In fact, a recent study from our institution (18) has shown that H_1 receptors mediate peripheral coronary vasodilation in patients without coronary artery disease but may induce large epicardial coronary artery constriction in patients with vasospastic angina, with or without organic narrowing.

However, the effects of histamine on the cardiovascular system in vivo are in part directly mediated by specific cardiovascular histamine receptors and in part by histamine-

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induced changes in factors that affect myocardial metabolic requirement, or by reflex increases in sympathoadrenergic activity and catecholamine release (2). It is therefore difficult to evaluate the direct effects exerted by histamine on the human coronary circulation in vivo.

The aim of the present study was twofold: 1) to evaluate the presence of a direct effect of histamine on the human coronary circulation by direct intracoronary histamine injection in a group of patients with angiographically normal coronary arteries; and 2) to assess the role of H_1 and H_2 receptors in this response by selective H_1 and H_2 blockade.

Methods

Study patients. The study group was composed of 10 patients whose clinical and angiographic data are shown in Table 1. All patients had normal coronary arteries, and no patient had a history of allergy, pheochromocytoma, peptic ulcer or chronic obstructive lung disease. Patients with cardiomyopathy or ventricular arrhythmia were also excluded. Patients were studied in the morning after an overnight fast and without premedication. All drugs, except sublingual nitrates when required, were discontinued for at least 5 half-lives. However, no patient consumed nitrates within 24 hours before the morning of the study. The study protocol was approved by the Ethics Committee of our institution and informed consent was obtained from each patient.

Study protocol. The study was initiated after completion of diagnostic coronary arteriography, performed by the Sones technique. Thirty minutes was allowed for a return to baseline hemodynamic conditions. Previous observations (7) have shown that contrast medium-induced changes in systemic and coronary hemodynamics are short-lasting.

During this interval, a 7F Wilton Webster catheter for the measurement of coronary blood flow by thermodilution (19) was advanced into the coronary sinus. Details of the technique utilized to maintain a correct position of the catheter throughout the study have been published elsewhere (18). An 8F Hemaquet sleeve was introduced into the brachial artery, and its lateral extension was connected to a Statham P23 Id transducer to allow continuous monitoring of arterial pressure. A 7.5F Sones catheter was advanced through the sleeve to the left coronary ostium and particular care was taken to ensure that it was in a stable position in the ostium.

Injection of histamine into the left coronary artery. After positioning the catheters, we started measuring baseline coronary blood flow and arterial pressure under continuous electrocardiographic (ECG) monitoring. Coronary blood flow was measured according to the technique described by Ganz et al. (19), by injecting saline solution into the distal coronary sinus through the thermodilution catheter at a constant rate of 60 ml/min with a Sage model 355 infusion pump. Thermistor signals, together with arterial pressure and ECG were recorded on an OTE multichannel polygraph at a paper speed of 100 mm/s. After 20 seconds of equilibration, while continuing coronary blood flow and arterial pressure recording, we started a 10 second injection of 5 ml of physiologic saline solution or 4 μg of histamine diluted in 5 ml of saline solution into the left coronary artery (Fig. 1). Event markers were recorded on paper in order to time exactly the point of onset and termination of intracoronary injection. Coronary blood flow, arterial pressure and ECG were continuously monitored during the 10 second injection and for 40 seconds after the end of the intracoronary injection.

Each patient received four separate intracoronary injections in the following order (Fig. 2): 1) intracoronary saline solution; 2) intracoronary histamine; 3) intracoronary histamine after H_2 receptor blockade with cimetidine; 4) intracoronary histamine after H_1 receptor blockade with diphenhydramine. After each intracoronary injection, 5 minutes

Table 1. Clinical and Angiographic Features of the 10 Study Patients With Normal Coronary Arteries

Patient	Age (yr) & Sex	Clinical Presentation	Risk Factor	TET	ET	Left Ventriculography		
						EDV(ml)	ESV(ml)	EF(%)
1	37F	Atypical angina	Smoking	+/−	—	83	10	88
2	55F	Atypical angina	HBP	—	ND	90	21	76
3	49M	Angina on effort	Smoking	+/−	—	158	58	63
4	37F	Atypical angina	—	ND	ND	—	—	—
5	53F	Atypical angina	—	+	ND	100	22	78
6	29F	Secundum ASD	—	ND	ND	90	35	61
7	48F	Angina on effort	HBP	—	—	83	10	88
8	37F	Atypical angina	Smoking	—	ND	125	46	63
9	44F	Mild MR + MS	HBP	ND	ND	205	97	52
10	23M	Atypical angina	Familial history	—	ND	138	53	61
Mean ± SD	41 ± 10					119 ± 42	39 ± 28	70 ± 13

ASD = atrial septal defect; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; ET = ergonovine test; HBP = high blood pressure; MR + MS = mitral regurgitation + stenosis; ND = not done; TET = treadmill exercise test; + = positive; − = negative; +/− = borderline.

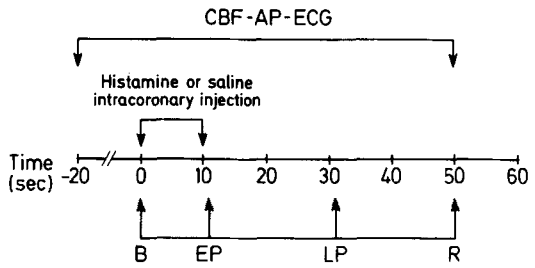


Figure 1. Schematic representation of the protocol used for each intracoronary injection of histamine or saline. AP = arterial pressure; B = baseline; CBF = coronary blood flow; ECG = electrocardiogram; EP = early period; LP = late period; R = recovery. See text for explanation.

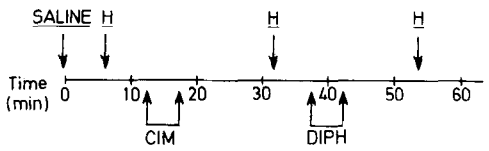
were allowed for hemodynamic return to baseline conditions. Cimetidine was given as a 400 mg intravenous bolus injection over 5 minutes and the second histamine injection was performed 15 minutes later. Diphenhydramine was given as a 10 mg intravenous bolus over 5 minutes and the third histamine injection was performed 10 minutes later. The intracoronary position of the tip of the Sones catheter was confirmed in all cases by the typical ST-T segment changes during intracoronary injection and by fluoroscopy at the end of injection.

In order to establish the consistency of the coronary hemodynamic response to repeated intracoronary histamine, we also studied, as a separate protocol, three additional patients with clinical and angiographic characteristics similar to those of the 10 patients reported in Table 1. The general protocol followed in these three patients was the same as that shown in Figures 1 and 2, but cimetidine and diphenhydramine were not administered.

There were no subjective complaints or complications with intracoronary administration of histamine. In particular, no pulsating headache or cutaneous flush was observed, nor were arrhythmias or conduction disturbances of any type recorded.

Measurements. RR interval (from the ECG recordings), mean arterial pressure (as diastolic plus one third of pulse pressure), coronary blood flow and coronary vascular resistance (derived as the ratio of mean arterial pressure to coronary blood flow) were measured just before the onset of each intracoronary injection, immediately after the injection (early period) and 30 seconds (late period) and 50 seconds (recovery) after the onset of the intracoronary injection (Fig. 1). RR intervals and the mean arterial pressure were measured as the average of 5 consecutive beats.

Figure 2. Schematic representation of the sequence of intracoronary injection of histamine (H) or saline solution in each patient. CIM = cimetidine; DIPH = diphenhydramine.



Coronary blood flow was calculated as follows: coronary blood flow = 60 × 1.08 × (Tb-Ti/Tb-Tm) − 1, where Tb, Ti and Tm = temperature of blood, injectate and blood-injectate mixture, respectively; 60 = coronary sinus injectate flow rate, and 1.08 = a constant accounting for the specific heat and density of blood and saline solution (19).

In seven patients we also measured from paper recordings the pre-ejection period/left ventricular ejection time ratio (PEP/LVET) and the relation between the electrical and mechanical systole, expressed as the QT/QD ratio, before and after the first intracoronary histamine injection, in the absence of H_1 and H_2 receptor blockade (QD = interval from Q wave to onset of diastole). These time intervals were measured at baseline, as the average value of the 5 beats immediately preceding the intracoronary histamine injection, and in the early period after histamine injection, as the average value of the 5 beats immediately following the end of the injection.

Left ventricular ejection time was measured from the onset of the upstroke of systolic arterial pressure to the dicrotic notch. Pre-ejection period was measured from the Q wave of the ECG to the onset of the upstroke of systolic arterial pressure, minus the delay in pulse transmission time from aortic root to brachial artery, that was measured in each of these seven patients at the beginning of the study. The QT interval was measured from the Q wave of the ECG to the termination of the T wave; in order to minimize errors in evaluating the termination of the T wave, at the beginning of the study the ECG lead with the sharpest delineation of this point was selected. The QD interval was measured from the Q wave of the ECG to the dicrotic notch of arterial pressure, minus the delay in pulse transmission time as previously evaluated.

Statistics. Statistical analysis was performed by Student's *t* test for paired samples. Results were expressed as percent change from baseline of all hemodynamic variables measured. Values were expressed as mean ± standard error of the mean (SEM). A p value of <0.05 was considered statistically significant.

Results

Figures 3 and 4 show the percent changes in RR interval, mean arterial pressure, coronary blood flow and coronary vascular resistance after intracoronary administration of saline solution, and intracoronary administration of histamine alone and after intravenous cimetidine and after intravenous diphenhydramine at the various time intervals of the study.

Changes in RR interval and mean arterial pressure (Fig. 3). No significant percent change in any hemodynamic variable was observed after intracoronary saline. The RR

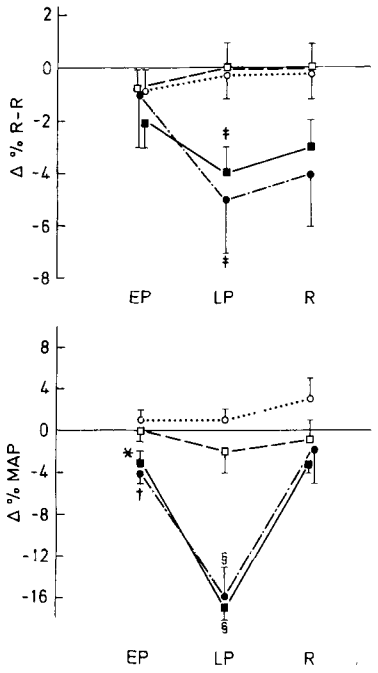


Figure 3. Percent changes in the RR interval and in the mean arterial pressure (MAP) after intracoronary injection of saline solution (□---□), histamine (■—■), histamine after cimetidine (●–·–●) and histamine after cimetidine + diphenhydramine (○···○). Other abbreviations as in Figure 1. Values are expressed as mean ± SEM. *$p < 0.05$, †$p < 0.02$, ‡$p < 0.01$, §$p < 0.001$ (vs. saline).

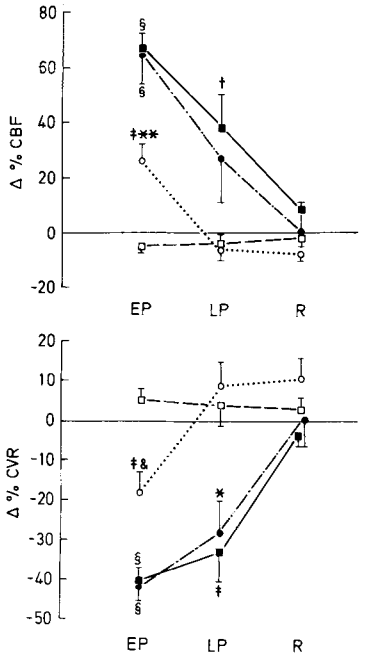


Figure 4. Percent changes in coronary blood flow (CBF) and coronary vascular resistance (CVR) after intracoronary injection of saline solution (□---□), histamine (■—■), histamine after cimetidine (●–·–●) and histamine after cimetidine + diphenhydramine (○···○). Other abbreviations as in Figure 1. *$p <$ 0.02, †$p < 0.01$, ‡$p < 0.005$, §$p < 0.001$ (vs. saline solution), **$p < 0.005$ and $p < 0.001$ (vs. histamine and histamine after cimetidine, respectively).

interval did not significantly change in the early period of any injection, but it decreased 4 ± 1% in the late period of histamine injection before blockade ($p < 0.01$ versus saline solution), and 5 ± 1% in the late period of histamine injection after cimetidine ($p < 0.01$ versus saline solution). The RR interval did not change significantly with intracoronary histamine after diphenhydramine, either in the late period or in the recovery phase. The mean arterial pressure (Fig. 3) decreased by 3 ± 1% in the early period of histamine injection without blockade ($p < 0.05$ versus saline solution) and by 4 ± 1% ($p < 0.02$ versus saline solution) in the early period of histamine injection after cimetidine, in both instances showing a marked fall in the late period (respectively by 17 ± 2% and 16 ± 3%, $p < 0.001$ versus saline solution), with a return to baseline in the recovery phase. No significant change in the mean arterial pressure was observed with histamine injection after diphenhydramine.

Changes in coronary hemodynamics (Fig. 4). Coronary blood flow increased 65 ± 6% in the early period of histamine injection without blockade and by 65 ± 11% after cimetidine (both $p < 0.001$ versus saline solution), with a return toward baseline in the late period and recovery phase of these two injections. With histamine after diphenhydramine, we observed a moderate but still significant percent increase in coronary blood flow in the early period (26 ± 6%, $p < 0.005$ versus saline solution) that was, however, lower than the increase observed with histamine before blockade and with histamine after cimetidine ($p <$ 0.005 versus the two previous injections). Coronary blood flow returned immediately to baseline in the late period and in the recovery phase.

Coronary vascular resistance decreased by 40 ± 3% in the early period of histamine injection before blockade and by 41 ± 4% after cimetidine (both $p < 0.001$ versus saline solution), in both instances remaining significantly lower than baseline in the late period and returning to baseline in the recovery phase. With histamine injection after diphenhydramine, we observed a slight but significant decrease of coronary vascular resistance in the early period (18 ± 5%, $p < 0.005$ versus saline solution) that was, however, lower than the decrease observed with the histamine injection before blockade and after cimetidine ($p < 0.001$). Coronary vascular resistance returned immediately to baseline in the late period and recovery phases of this injection.

Figure 5 shows the mean percent increase in coronary blood flow in the early period after intracoronary histamine injection in three patients who received three consecutive intracoronary histamine injections without H_2 or H_1 receptor blockade. There was no statistically significant difference

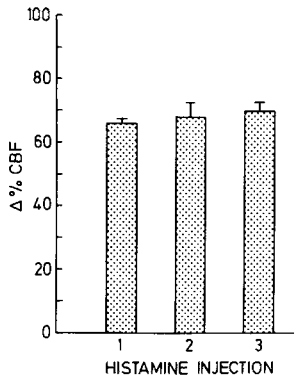


Figure 5. Mean percent increase in coronary blood flow (CBF) in the early period immediately after intracoronary histamine injection in three patients who received three consecutive intracoronary histamine injections without H_2 and H_1 receptor blockade.

among the three injections in the percent increase in coronary blood flow immediately after intracoronary histamine.

Changes in PEP/LVET and QT/QD ratio (Table 2). No statistically significant difference was found between baseline and postinjection values of the PEP/LVET and QT/QD ratios before and immediately after the first intracoronary histamine injection.

Discussion

Direct coronary hemodynamic effects of histamine. Earlier observations in experimental animals (5–9) and in vitro findings obtained on human coronary arteries (17) showed a direct effect of histamine on coronary vasomotion. We have demonstrated that intravenous histamine produces H_1-mediated coronary vasodilation that can be attributed, at least in part, to reflex cardiovascular changes secondary to histamine-induced hypotension (18).

Table 2. Changes in Individual and Mean (± SEM) Values of PEP/LVET and of QT/QD Ratio With Intracoronary Histamine Injection

	PEP/LVET		QT/QD	
Patient	B	H	B	H
1	0.406	0.398	0.90	0.87
2	0.374	0.308	0.89	0.91
3	0.302	0.256	0.94	0.86
4	0.306	0.290	1.03	0.98
5	0.302	0.259	1.06	1.06
6	0.210	0.203	1.00	1.05
7	0.188	0.210	1.00	0.98
Mean ± SEM	0.298	0.274	0.97	0.96
	0.07	0.06	0.06	0.08
	NS		NS	

B = baseline; H = immediately after intracoronary histamine injection; NS = not significant; PEP/LVET = pre-ejection period/left ventricular ejection time ratio; QT/QD = ratio of electrical to mechanical systole.

The present study shows that in patients with normal coronary arteries and without vasospastic angina, histamine induces a direct coronary vasodilator effect that is independent of changes in the determinants of myocardial oxygen consumption. In fact, without H_1 and H_2 blockade, coronary vascular resistance decreased and coronary blood flow increased immediately after intracoronary histamine injection (early period phase), when no change in the RR interval (and thus in heart rate) and no increase or even a small reduction in arterial pressure had occurred. Because heart rate and arterial pressure are two of the major determinants of myocardial oxygen consumption (20), these data indicate a histamine induced dilation of small coronary resistance vessels independent of enhanced myocardial metabolic requirements.

It is unlikely that other factors that affect myocardial oxygen consumption, such as catecholamine release or changes in left ventricular contractility or volume, may have played a role in this early coronary vasodilation. Although histamine can directly enhance left ventricular contractility through H_2 receptors (21) or indirectly through a histamine-induced catecholamine release and stimulation of $beta_1$ adrenergic receptors (22), this is unlikely to have occurred because the PEP/LVET ratio, an index well reflecting directional variations in left ventricular inotropism (23), did not significantly change in the early phase after intracoronary histamine. In addition, H_2 receptor blockade by cimetidine did not modify the coronary hemodynamic response to intracoronary histamine (Fig. 4), nor did we observe any change in QT/QD, a ratio well reflecting autonomic tone variations at the myocardial level and thus sensitive to sympathetic stimulation of the left ventricle (24). Catecholamine-induced pharmacologic coronary vasodilation is also unlikely because vasoconstrictor $alpha_2$ adrenergic receptors are predominant in coronary artery smooth muscle (25). Therefore, the coronary vasodilation observed immediately after intracoronary histamine is likely due to a direct vasodilator effect of histamine on small coronary resistance vessels.

Receptor mechanism underlying the direct coronary hemodynamic effects of histamine. Studies (17) on human coronary arteries in vitro have shown that histamine induces H_1-mediated constriction and H_2-mediated vasodilation of large epicardial coronary arteries. However, these experimental studies cannot be extrapolated to humans in vivo because they are limited to the effects of histamine on large capacitance coronary arteries and do not take into account the multiple factors capable of affecting coronary vasomotion in vivo. In this respect, recent in vivo studies (18,26) have suggested that activation of H_1 receptors might provoke epicardial coronary constriction or spasm in a subset of patients with variant angina with or without atherosclerotic narrowing, while inducing dilation of resistance coronary vessels in patients with normal coronary arteries (18). How-

ever, these studies were based on systemic histamine administration and, therefore, could not separate the systemic from the coronary hemodynamic effects of histamine.

In the present study, the effects of repeated intracoronary histamine injections after selective histamine receptor blockade suggest that the direct coronary vasodilator effect of histamine is mediated by H_1 receptor activation because diphenhydramine, but not cimetidine, significantly decreased the histamine-induced decrease in coronary vascular resistance. The latter can hardly be attributed to acute desensitization to the coronary vasodilator effect of histamine because three consecutive intracoronary histamine injections without H_2 or H_1 receptor blockade in three patients produced the same consistent coronary vasodilator effect (Fig. 5). These data confirm and extend to humans the finding that H_1 receptor activation produces peripheral vasodilator effects in several vascular regions, including the coronary region (6,8,9,27,28), and suggest that, in contrast to what has been reported for other vascular districts (29), H_2 receptors do not play a major role in the peripheral coronary vasodilation induced by histamine.

The slight but significant peripheral coronary vasodilation persisting even after combined H_2 and H_1 blockade suggests that part of the direct vasodilator effect of histamine is independent of the known H_1 and H_2 receptor mechanisms. It is unlikely that this persistent vasodilation is mediated by the activation of the H_3 receptor recently described in the brain (30). An incomplete H_1 and H_2 receptor blockade, allowing a persistent coronary dilation even after the third histamine injection, can be ruled out by the prevention of heart rate and arterial pressure changes with histamine injection after combined cimetidine and diphenhydramine pretreatment. However, our data do not allow us to hypothesize any mechanism or mechanisms responsible for the coronary dilation persisting after combined H_1 and H_2 receptor blockade.

Systemic hemodynamic effects of intracoronary histamine. Histamine injected by the intracoronary route produces its typical effects, represented by tachycardia and hypotension (1,2), on systemic hemodynamics. These effects are mediated in large part by H_1 receptors because they are not modified by cimetidine, but are prevented by diphenhydramine. Although a previous study (1) showed that systemic hypotension after histamine administration is mediated by both H_1 and H_2 receptors, H_1 receptors are predominantly involved in the systemic hypotensive response to a bolus injection of small doses of histamine as used in our study (31).

The slight decrease in arterial pressure in the early phase of intracoronary injection of preblockade histamine and postcimetidine histamine might be due to a negative inotropic effect of histamine mediated by H_1 receptors (32) because it persisted after cimetidine but was abolished by diphenhydramine. However, we cannot discount that a role might have been played by a small amount of histamine that escaped the intracoronary route and reached the peripheral circulation.

The tachycardic response to histamine can be attributed to a direct histamine effect on the sinus node through H_2 receptors (4) or to a reflex sympathoadrenergic activation (2). The present study supports the latter hypothesis because no change in the RR interval was observed in the early period after intracoronary histamine, when coronary hemodynamic changes had already occurred, in those patients with a sinus node artery arising from the circumflex coronary artery. In all patients the reduction in the RR interval paralleled the fall in systemic arterial pressure, thus suggesting a reflex sympathoadrenergic activation.

Possible limitations of the study. The conclusions reached in our study, that histamine mediates small vessel coronary vasodilation through H_1 receptors in patients with normal coronary arteries and without evidence of vasospastic angina, should not be extrapolated to patients with coronary artery disease or vasospastic angina. In fact, in a percentage of these patients, H_1 receptor activation may mediate vasoconstriction or spasm of large epicardial coronary arteries (18,26). In addition, we cannot exclude the possibility that the effects of endogenous histamine released locally within the vessel wall (11,13,15) in anaphylactic reactions might differ quantitatively or qualitatively from those outlined in our study.

Finally, because we did not investigate the change in diameter of proximal coronary arteries, we cannot rule out that, as shown in in vitro studies (16,17), H_1 receptor stimulation may induce vasoconstriction of large epicardial coronary arteries. However, it is unlikely that mild proximal coronary constriction, should it have occurred, might have influenced the coronary hemodynamic changes found in our patients, because in the absence of coronary artery disease or vasospastic angina, coronary vascular resistance is greatly influenced by the tone of small coronary arterioles (7).

Clinical implications. Our results might have relevance for a better understanding of coronary hemodynamic changes in patients without coronary artery disease or vasospastic angina during systemic histamine release in the course of anaphylactic or anaphylactoid reactions (3,12). These reactions are occasionally associated with ECG signs of myocardial ischemia or with myocardial infarction (33–35). Our findings suggest that these events are not secondary to a direct coronary effect of histamine, even in patients taking H_2 receptor blocking drugs, because in these patients H_1 receptor stimulation is more likely to induce peripheral coronary vasodilation. Although we cannot rule out a proximal coronary vasoconstrictor effect of H_1 receptor stimulation, this cannot be to such an extent as to counterbalance the peripheral coronary vasodilation. It is more likely that ischemic events during anaphylactic reactions in patients with normal coronary arteries are secondary to the systemic ef-

fects of histamine or to the release of other chemical mediators of anaphylaxis, such as leukotrienes or platelet-activating factor, which are able to produce a marked derangement of cardiovascular function (36,37).

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